THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Hypertrophic Cardiomyopathy

Present and Future, With Translation Into Contemporary Cardiovascular Medicine

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a common inherited heart disease with diverse phenotypic and genetic expression, clinical presentation, and natural history. HCM has been recognized for 55 years, but recently substantial advances in diagnosis and treatment options have evolved, as well as increased recognition of the disease in clinical practice. Nevertheless, most genetically and clinically affected individuals probably remain undiagnosed, largely free from disease-related complications, although HCM may progress along 1 or more of its major disease pathways (i.e., arrhythmic sudden death risk; progressive heart failure [HF] due to dynamic left ventricular [LV] outflow obstruction or due to systolic dysfunction in the absence of obstruction; or atrial fibrillation with risk of stroke). Effective treatments are available for each adverse HCM complication, including implantable cardioverter-defibrillators (ICDs) for sudden death prevention, heart transplantation for end-stage failure, surgical myectomy (or selectively, alcohol septal ablation) to alleviate HF symptoms by abolishing outflow obstruction, and catheter-based procedures to control atrial fibrillation. These and other strategies have now resulted in a low disease-related mortality rate of <1%/year. Therefore, HCM has emerged from an era of misunderstanding, stigma, and pessimism, experiencing vast changes in its clinical profile, and acquiring an effective and diverse management armamentarium. These advances have changed its natural history, with prevention of sudden death and reversal of HF, thereby restoring quality of life with extended (if not normal) longevity for most patients, and transforming HCM into a contemporary treatable cardiovascular disease. (J Am Coll Cardiol 2014;64:83–99) © 2014 by the American College of Cardiology Foundation.

More than 50 years have elapsed since the modern pathological description of hypertrophic cardiomyopathy (HCM) by Teare in 1958 (1), followed shortly thereafter by the first detailed clinical reports from Dr. Eugene Braunwald and colleagues at the National Institutes of Health (Bethesda, Maryland) in the early 1960s (2). For much of the early years, HCM was considered a rare, interesting, and perhaps odd (if not exotic) disease, with high mortality and little effective or safe treatment interventions. In particular, measures to prevent sudden death (SD), undoubtedly the most feared and visible complication of this complex genetic disease, were unavailable to young patients for decades. In a very early (1962) paper that defined left ventricular (LV) outflow tract obstruction in HCM, Dr. Braunwald wrote: "At this time, we are aware of no method of management that can specifically and favorably influence the course of a patient" (3).

As major reviews of HCM have appeared over the last decade (4-13), changes in the clinical profile, diagnostic methods, and management options have continued and accelerated, including: 1) recognition

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of the full diversity of the disease spectrum, which is now recognized as associated with a relatively low adverse event rate (14-22); 2) definition of the molecular basis of the disease, with the opportunity for family screening and identification of relatives not at risk for developing HCM, as well as affected family members without clinical evidence of disease (12,23-26); 3) introduction of implantable cardioverter-defibrillators (ICDs) for prevention of SD (27-31); 4) development of a more reliable stratification model, expanding recognition and appreciation of the highest-risk patients who will most likely benefit from ICDs (8,32-34); 5) penetration of advanced imaging into HCM practice with high-resolution and tomographic cardiovascular magnetic resonance (CMR) imaging (Fig. 1), complementary to echocardiography, with improved diagnosis and identification of novel at-risk subgroups, expanding the scope of risk stratification (9,17,19,35); 6) advances in operative (myectomy) techniques, resulting in low-risk surgery that is highly effective in abolishing outflow obstruction and heart failure (HF) symptoms (10,13,36); 7) introduction of nonsurgical alternatives to myectomy for selected patients, such as percutaneous alcohol septal ablation (37); 8) recognition of the impact of patient age in dictating clinical course and management decisions (38); 9) publication of comprehensive guidelines offering concise and specific recommendations to the practicing community for diagnosis and management (39,40); 10) advances in refractory HF treatment, including transplantation (18); 11) recognizing the significant cardiovascular mortality benefit attributable to contemporary treatment options (27,28,41); and 12) evolution in the perception of HCM to a disease deserving of a more optimistic outlook, compatible with extended longevity for most patients and affording them with a measure of reassurance (42).

These advances for patients with HCM support this State-of-the-Art review, which is designed to provide the cardiovascular community with an opportunity to appreciate the important current approaches to this complex disease. This is a clinically relevant, patient care-related discussion formulated around contemporary HCM practice patterns, assembled by the efforts of 6 expert cardiologists with established dedication to HCM and care of these patients. The presentation is structured around 7 major areas: epidemiology; genetics and genetic testing; clinical diagnosis with imaging; natural history and impact of

therapy; risk stratification and prevention of SD; HF management, septal reduction therapy, and transplantation; and the role and significance of atrial fibrillation (AF).

HCM remains a challenging disease, characterized by a heterogeneous clinical profile and considerable unpredictability in its natural history, with clinical decisions often made without absolute certainty on the basis of incomplete data.

EPIDEMIOLOGY

Although once considered rare, HCM is now more appropriately regarded as the most common inherited cardiac disease. A number of population studies estimate the prevalence of HCM in the general population to be at least 1 in 500, with the extrapolation that 700,000 Americans are affected by this disease (43).

HCM is a global disease, reported in >50 countries on all continents, including the most populous nations of India and China (7). Consequently, HCM is known to occur in a variety of races and ethnic groups (44), as well as equally in both sexes and with a generally similar clinical, phenotypic, and genetic expression (45).

Paradoxically, the estimated prevalence of HCM in the general population seems inconsistent with the persistent perception in cardiovascular practice that it is a distinctly uncommon disease. This apparent discrepancy strongly suggests that most affected individuals are not diagnosed clinically, probably achieving advanced longevity without HCM-related symptoms. Therefore, clinicians assess only a small fraction of the overall HCM population (likened to the "tip of the iceberg"), which often includes patients who are diagnosed only because of symptoms or clinical events (46). Fortuitous diagnosis of HCM during routine clinical or family screening and evaluation is increasing due to unexpected findings on electrocardiography (ECG) or advanced imaging (47).

GENETICS

GENERAL PRINCIPLES. It has been almost 25 years since the seminal work by the Seidman laboratory and others identified the first sarcomere gene mutations that cause HCM, bringing this genetic disease into the modern era of molecular investigation (25). HCM is inherited with an autosomal dominant Mendelian pattern, variable expressivity, and age-related (and incomplete) penetrance (12,25,48-50). Offspring of an affected individual have a 50% probability of inheriting a mutation and risk for the disease; alternatively, sporadic cases may be due to de novo
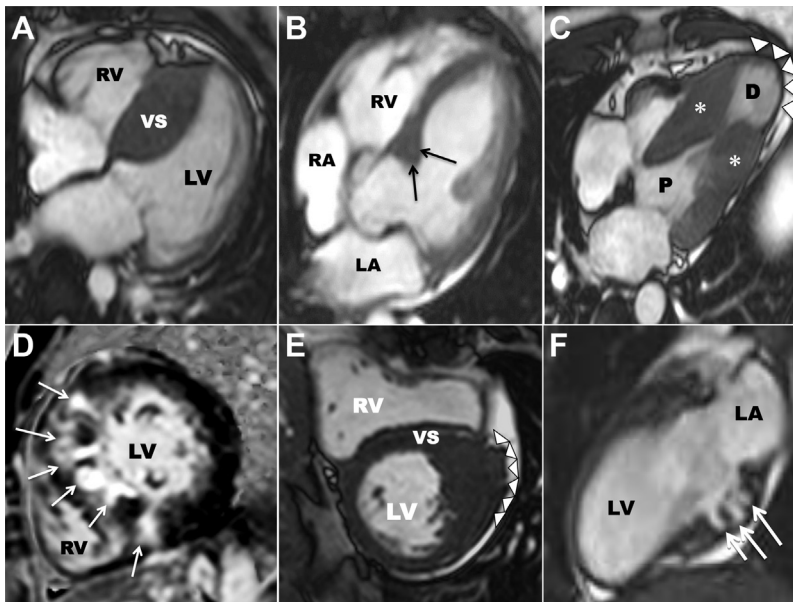
FIGURE 1 Cardiovascular Magnetic Resonance Images Demonstrate Diversity of the Hypertrophic Cardiomyopathy Phenotype

(A) Asymmetric hypertrophy of ventricular septum (VS), sparing the left ventricular (LV) free wall. **(B)** Focal hypertrophy sharply confined to basal anterior septum **(arrows)**. **(C)** Thin-walled apical aneurysm **(arrowheads)** with muscular mid-ventricular apposition of hypertrophied septum and LV wall **(asterisks)**, and distinct proximal (P) and distal (D) chambers. Adapted with permission from Maron et al. (19).
(D) Extensive, transmural late gadolinium enhancement involving ventricular septum **(arrows)**. **(E)** Massive thickening (i.e., 33 mm) confined largely to anterolateral LV wall, greatly underestimated by echocardiography **(arrowheads)**. Adapted with permission from Maron et al (9).
(F) Genotype positive-phenotype negative HCM family member with 3 myocardial crypts penetrating thickness of basal inferior wall **(arrows)**. Adapted with permission from Maron et al. (55). LA = left atrium; RA = right atrium; RV = right ventricle.

mutations present in the proband, but which are absent in the parents (12,25,48–50).

To date, a large number of genetic studies have established that HCM is caused by mutations in 11 or more genes encoding thick and thin contractile myofilament protein components of the sarcomere, or adjacent Z-disc, which are expressed primarily or exclusively in the heart (12,25,48–50) (**Fig. 2**). Approximately, 70% of successfully genotyped patients are found to have mutations in the 2 most common genes, beta-myosin heavy chain and myosin-binding protein C, whereas several other genes are much less common, accounting for <5% of patients (**Fig. 2**).

The genetic heterogeneity of HCM has proved daunting, now with more than 1,500 individual mutations (90% missense mutations) identified among the known genes, most of which appear to be "private" and unique to individual families (12,25). This vast genetic heterogeneity of HCM, perhaps more than any other factor, has limited the role of mutational analysis in predicting prognosis (or

phenotypic expression) for individual patients (**Central Illustration**).

GENETIC TESTING RESULTS. Although initially confined to research settings, numerous commercial laboratories and academic centers now offer comprehensive (usually fee-for-service) genetic testing panels using rapid and automated DNA-sequencing to identify HCM-causing mutations and provide a molecular diagnosis (12). Despite early optimism that "malignant" or "benign" mutations would be identifiable among patient populations (25), more recent clinical genetic studies have shown that using single nucleotide sarcomere mutations to judge prognosis or predict outcome is unreliable for individual patients (4,12,40). Therefore, genetic testing in HCM does not influence treatment strategies and specifically does not identify high-risk patients who may benefit from ICD therapy (4,12,27,28,40).

Clinical utility of genetic testing. The most compelling reason to specifically consider genetic testing in clinical practice is to identify family members affected by HCM, but without left ventricular
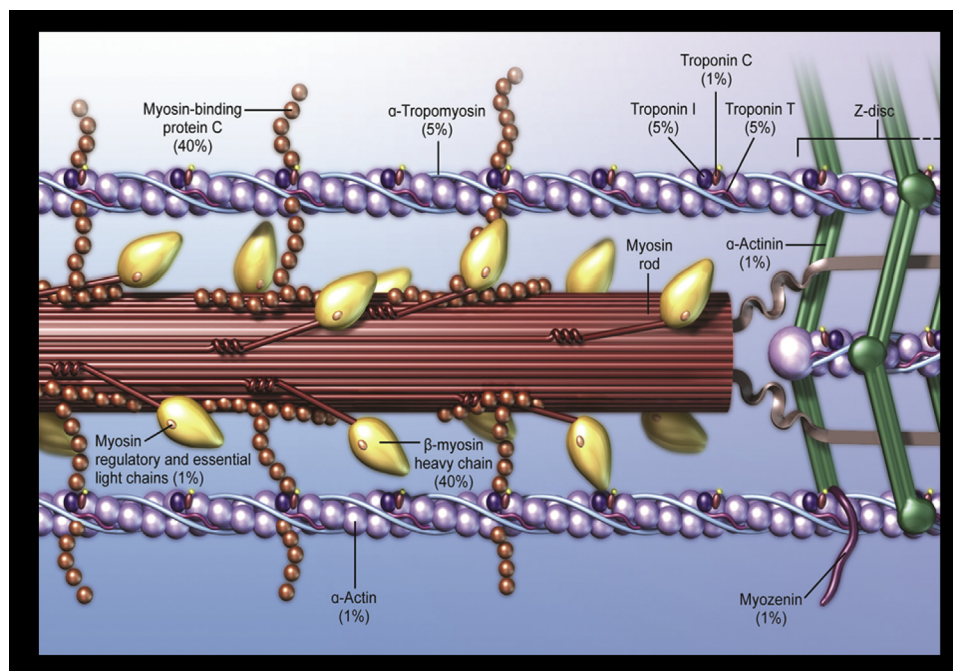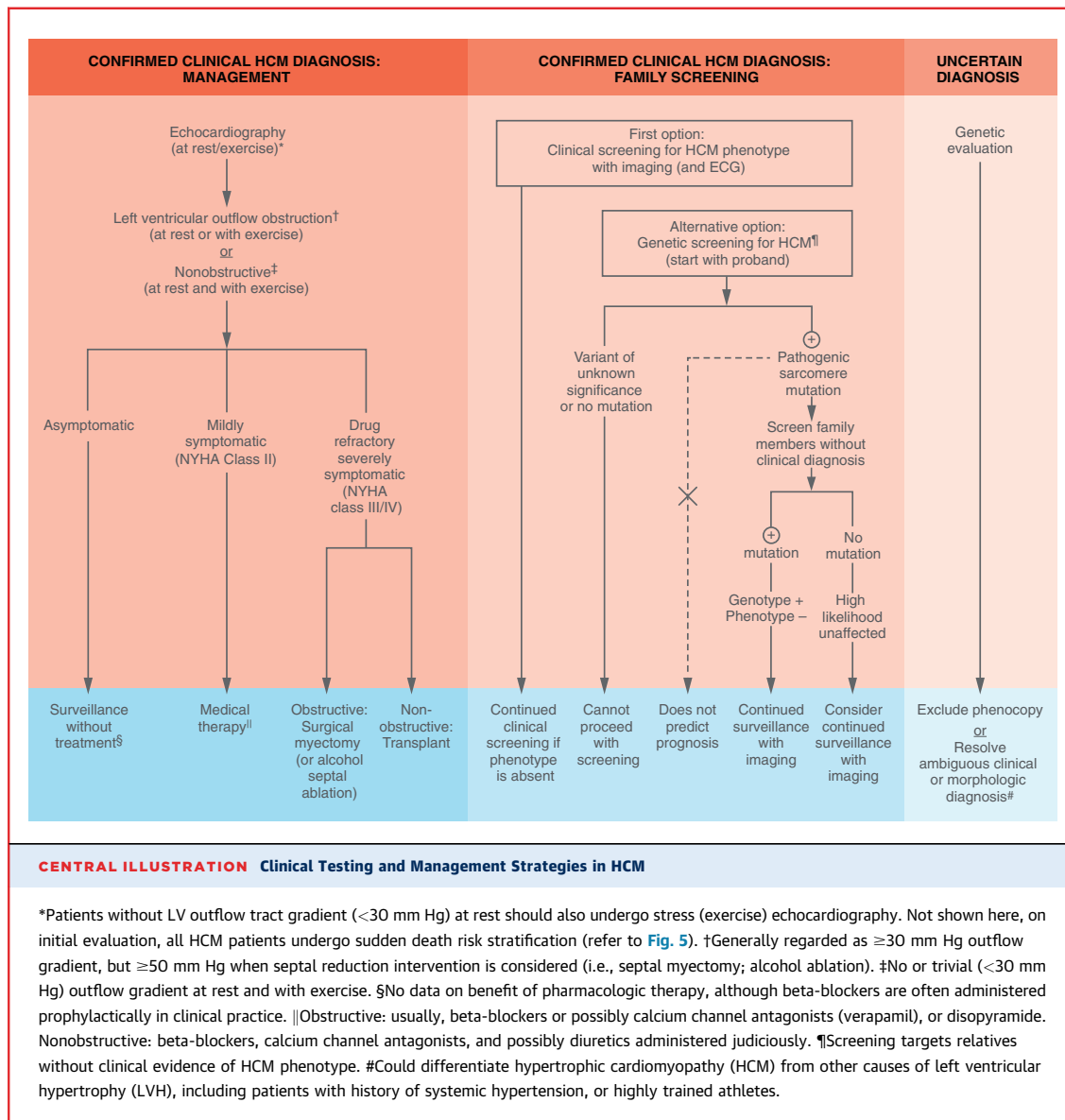
FIGURE 2 Genetics and Family Screening Strategies in HCM

Cardiac sarcomere showing the location of known HCM disease-causing genes. Prevalence for each of the 11 genes derived from studies in unrelated HCM probands with positive genotyping are shown in parentheses. Not shown are genes previously linked to HCM, but with lesser evidence for pathogenicity: α-myosin heavy chain, titin, muscle LIM protein, telethonin, vincalin/metavinculin, junctophilin 2. Adapted with permission from Maron and Maron (4).

hypertrophy (LVH), who nevertheless may be at risk for developing this disease (**Central Illustration**). Notably, in practical terms, the genetic testing screening strategy requires successful identification of a pathogenic (disease-causing) sarcomere mutation in a clinically expressed HCM proband. However, the likelihood that a pathogenic mutation will be found in the proband is only 35% overall (although somewhat higher with positive family history) (4,12,48-50). When a pathogenic mutation is identified in a family member, the genetic status of all other relatives can be interrogated; those who did not inherit the genetic abnormality found in the proband have a very low risk for developing the disease (4,12).

HCM GENOTYPE WITHOUT LVH. Relatives identified with pathogenic mutations but without evidence of the disease phenotype comprise a new HCM subgroup, designated as genotype positive-phenotype negative (24,40,51,52) (**Central Illustration**). Such individuals demonstrate the principle that any absolute LV wall thickness is compatible with HCM. The precise risk of eventually developing LVH in this group remains uncertain, largely due to the relatively short period

of time that commercial genetic testing has been widely accessible. Nevertheless, although phenotypic conversion is probably common, it is also possible that some relatives may never develop hypertrophy (i.e., incomplete penetrance). However, ECG abnormalities and subclinical diastolic dysfunction can be noninvasive markers for future development of LVH in gene carriers. In addition, despite the absence of LVH, gene carriers may show various LV morphologic abnormalities, including fibrosis imaged by contrast CMR, collagen biomarkers, mitral leaflet elongation, and blood-filled crypts (4,53-55). If identified in a relative of a HCM patient, these markers suggest affected status, and emphasize the importance of formal genotyping to achieve a definitive HCM diagnosis, as well as close follow-up for detecting development of clinical disease with LVH. There is no compelling evidence that genetically affected relatives without LVH are at increased risk of SD (12,51,52,56), and Bethesda Conference #36 consensus recommendations do not exclude genotype positive-phenotype negative individuals from competitive sports (57).

CENTRAL ILLUSTRATION Clinical Testing and Management Strategies in HCM

*Patients without LV outflow tract gradient (<30 mm Hg) at rest should also undergo stress (exercise) echocardiography. Not shown here, on initial evaluation, all HCM patients undergo sudden death risk stratification (refer to Fig. 5). †Generally regarded as ≥30 mm Hg outflow gradient, but ≥50 mm Hg when septal reduction intervention is considered (i.e., septal myectomy; alcohol ablation). ‡No or trivial (<30 mm Hg) outflow gradient at rest and with exercise. §No data on benefit of pharmacologic therapy, although beta-blockers are often administered prophylactically in clinical practice. ‖Obstructive: usually, beta-blockers or possibly calcium channel antagonists (verapamil), or disopyramide. Nonobstructive: beta-blockers, calcium channel antagonists, and possibly diuretics administered judiciously. ¶Screening targets relatives without clinical evidence of HCM phenotype. #Could differentiate hypertrophic cardiomyopathy (HCM) from other causes of left ventricular hypertrophy (LVH), including patients with history of systemic hypertension, or highly trained athletes.

DEFINING PATHOGENICITY. Mutations are assigned pathogenic (or likely pathogenic) status on a probabilistic basis—not necessarily as a definitive yes or no (12,58)—using the preponderance of evidence available from a variety of criteria, including previous reports that a given mutation has caused HCM in other families (12). If the genetic test in the proband is negative for a sarcomere mutation, or alternatively a novel DNA sequence variant for which pathogenicity is unresolved (i.e., "variant of unknown significance") is reported, then this testing strategy cannot be applied to determine whether other relatives are genetically affected. Increasing numbers of ambiguous variants identified with comprehensive DNA next-generation sequencing could further confuse interpretation of genetic screening results, underscoring the challenges for translating complex molecular science to patient care in HCM (12). Although not widely recognized by clinicians, there is a possibility, in up to 10% of probands, that the classification of any variant can be re-interpreted over time, as new information becomes accessible (59), causing the reassessment of genetic testing implications for a family.

DIFFERENTIAL DIAGNOSIS. Notably, genetic testing has the unique potential to clarify diagnosis in some patients with metabolic storage diseases (i.e., PRKAG2, Fabry disease, LAMP2 cardiomyopathy [Danon disease]), which differ from sarcomeric HCM with respect to pathophysiology, natural

history and management, but share similar clinical expression and the pattern of LVH (**Central Illustration**). For example, genetic testing is crucial for diagnosis of LAMP2, which has a lethal natural history (survival uncommon at >25 years of age) that requires early recognition and usually intervention with heart transplantation (60). Genetic testing is also crucial for Fabry disease, which has a different treatment algorithm, with primary enzyme replacement.

CLINICAL FAMILY SCREENING. Screening for HCM is universally recommended for families. The first option for assessment of family members is usually clinical screening with imaging tests (echocardiography and CMR) and ECG (**Central Illustration**). This strategy is usually initiated during adolescence, the time at which the development of LVH most often occurs in HCM (4,6,12,23,26,39,40). Therefore, for relatives, echocardiographic screening most often begins at approximately 12 years of age, continuing thereafter at 12- to 18-month intervals, until full physical maturity is achieved between 18 and 20 years of age (23,39,40). Because of the rare possibility of adult onset hypertrophy and phenotypic conversion later in life between 20 and 50 years of age, further serial imaging at approximately 5-year intervals may be appropriate (26,61). It would be advantageous to consider screening with CMR, particularly if the 12-lead ECG is abnormal, because in some patients, segmental areas of LVH may be identifiable only with high-resolution tomographic CMR (9).

Furthermore, all HCM patients and relatives should have access to some form of genetic counseling, including discussion of testing results, risks and/or benefits, and options (12). Certified genetic counselors play an important role in collecting data to facilitate cosegregation studies and clarifying pathogenicity of mutations, as well as organizing family discussions to mitigate psychosocial impact of inheriting a potentially deleterious disorder (56). In the United States, many HCM patients are evaluated in settings where the multidisciplinary model incorporating cardiologists and counselors into one program can be difficult to create.

CLINICAL DIAGNOSIS AND HCM PHENOTYPE: CONTEMPORARY IMAGING

HCM WITH LVH. Clinical diagnosis of HCM requires confirmation with cardiac imaging of phenotypic expression, that is, an unexplained increase in LV wall thickness (≥15 mm in adults) associated 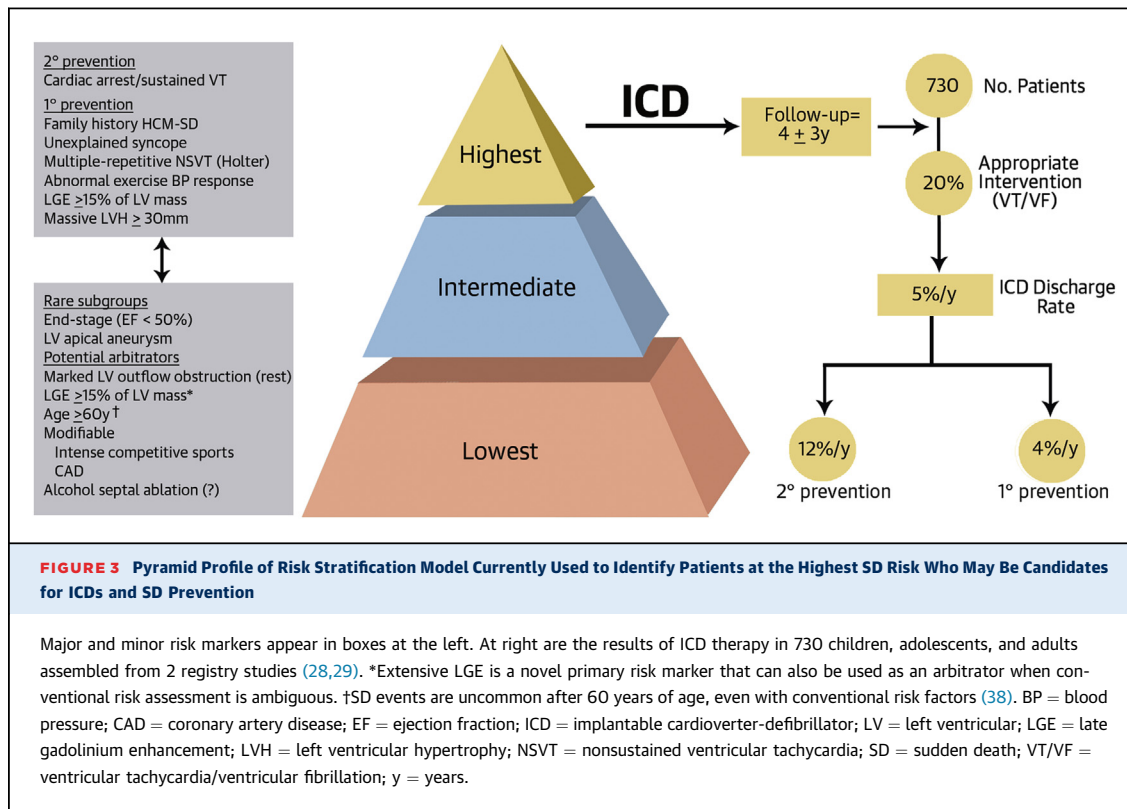with a nondilated LV chamber (4,9,57,62). Lesser degrees of wall thickness (i.e., 13 to 14 mm) can also be diagnostic of HCM, particularly when identified in family members (4,9). Since the early 1970s, echocardiography has been the mainstay for imaging the HCM phenotype (63), and it remains the initial test for patients due to its portability, widespread access, and reliability in quantifying dynamic outflow tract gradients (62).

More recently, CMR has emerged as a powerful complementary tool due to its unique strengths of tomographic imaging and enhanced spatial resolution, which affords better characterization of the complex HCM phenotype. Specifically, CMR provides an opportunity to provide more precise LV wall thickness measurements and improved risk stratification by imaging myocardial scars (i.e., late gadolinium enhancement) (35) (**Fig. 1**). In selected patients, CMR may be the sole method for reliably confirming the HCM phenotype and diagnosis, particularly when increased wall thickness is confined to specific areas of the LV chamber, such as the anterolateral free wall and apex (9,64). Underestimation of LV wall thickness by echocardiography (with respect to CMR) may have management implications (9), particularly in patients with massive LVH, which is an independent SD risk factor in HCM (65).

Furthermore, CMR provides a more complete interrogation of HCM morphology, including right ventricular hypertrophy, high-risk LV apical aneurysms with regional scarring, and abnormalities that may contribute to subaortic obstruction (i.e., elongated mitral valves, aberrant papillary muscles, and accessory muscle bundles), as well as anomalous insertion of anterolateral papillary muscle directly into the mitral valve, producing mid-cavitary muscular obstruction (4,9,17,19,22,66). CMR also may allow differentiation of apical HCM from LV noncompaction.

Although a wide range in maximal LV wall thicknesses up to >50 mm are consistent with HCM (9,62), an important minority of patients (10% to 20%) show relatively mild degrees of LVH evident in localized segments of the chamber (9,64), and with normal CMR-calculated LV mass (67). This underscores the principle that increased LV mass is not a prerequisite for a HCM diagnosis.

Virtually any asymmetric pattern of LVH can be observed in phenotypically expressed HCM, with maximum wall thickening found at virtually any location (9,62), but most commonly at the confluence of the anterior septum and contiguous anterior free wall (9). Specific patterns of LVH do not predict outcome, although mild localized wall thickening is generally associated with lower risk, independent of

FIGURE 3 Pyramid Profile of Risk Stratification Model Currently Used to Identify Patients at the Highest SD Risk Who May Be Candidates for ICDs and SD Prevention

Major and minor risk markers appear in boxes at the left. At right are the results of ICD therapy in 730 children, adolescents, and adults assembled from 2 registry studies (28,29). *Extensive LGE is a novel primary risk marker that can also be used as an arbitrator when conventional risk assessment is ambiguous. †SD events are uncommon after 60 years of age, even with conventional risk factors (38). BP = blood pressure; CAD = coronary artery disease; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LGE = late gadolinium enhancement; LVH = left ventricular hypertrophy; NSVT = nonsustained ventricular tachycardia; SD = sudden death; VT/VF = ventricular tachycardia/ventricular fibrillation; y = years.

its location (65). The absence of hyperdynamic systolic function, systolic anterior motion of the mitral valve, or myocardial scarring on CMR does not exclude a HCM diagnosis. Extrinsic factors, such as obesity, may influence primary phenotypic expression of HCM (including LV mass) and HF symptoms (68).

CLINICAL COURSE AND NATURAL HISTORY

HCM is perhaps unique among cardiovascular diseases by virtue of its potential for identification, clinical presentation, and progression during all phases of life, from infancy to advanced age. This long period of observation can itself impede complete understanding of the natural history of HCM over the many decades of life.

In the last 10 to 15 years, considerable clarity has emerged regarding HCM from large retrospective and/or observational cohort studies in a number of institutions and multicenter populations. It is evident that HCM is frequently compatible with normal life expectancy, often without functional disability or disease-related events, nor the necessity for major therapeutic interventions (4,14,39,40,42). This is a source of reassurance to many patients

regarding their prognosis. Not uncommonly, HCM patients survive to 70, 80, and even >90 years of age (69), often with no or mild symptoms, reaching statistical longevity similar to that of age and sex-matched general populations. This underscores the principle that mortality in most HCM patients is ultimately attributable to non-HCM and non-cardiovascular causes.

Nevertheless, subgroups at risk for important disease complications and premature death reside within the overall HCM population (**Fig. 3**). Patients may be situated in, or progress to, specific adverse pathways, with the natural history of their disease punctuated by events that may be the target of specific treatment strategies: 1) risk of SD; 2) progressive HF with exertional dyspnea and functional limitation (with or without chest pain); or 3) paroxysmal or chronic AF.

Reported HCM-related mortality risk has undergone substantial revision over time. For example, 25 years ago, HCM was regarded as a particularly high-risk disease with an annual mortality of 4% to 6%, based largely on patient populations from a few highly selected tertiary referral centers of a previous era (70-72). Patient selection bias in such

programs effectively overestimated the risk of HCM (73), contributing to the reputation of this disease as one with a grim prognosis and little expectation for longevity, a myth that may still persist today.

In the 1990s, reports from patient cohorts characterized by less selectivity, adjusted expected HCM mortality rates to about 1.5%/year (14). However, by utilizing contemporary and aggressive treatment interventions (particularly the ICD and heart transplantation), mortality in adult patients has further decreased to about 0.5% per year (41), thereby transforming HCM into a treatable condition with low disease-related mortality. Furthermore, because the SD rate has decreased due to increasing penetration of ICDs into HCM practice, death due to HF is emerging as the predominant mode of demise.

Patient age itself is an important determinant of HCM-related event rates and clinical course. For example, SD events are most common in young patients <30 years of age (4-6,8,15), but paradoxically, SD is very uncommon in patients of more advanced ages (>60 years) (38), even among those with acknowledged risk factors. In this age group, HCM appears to have a more benign expression and a lower risk status by virtue of decades of stability and survival. Both sexes have similar SD risk, although women are diagnosed later in life, often with more advanced HF symptoms (45).

However, the unpredictability of the HCM disease process requires regular (usually annual) surveillance to monitor potential clinical and/or risk profile changes. The most advantageous outcomes may derive from engagement in multidisciplinary-dedicated HCM centers, in which all management options (and expert operators) are available within the same institution (74,75). Such treatment opportunities, which have dramatically changed the outlook for many HCM patients, may not yet be readily available (or even a realistic aspiration) for patients in many parts of the world. For example, the vast number of HCM patients in the most populous countries (i.e., India and China) do not have access to robust personal medical insurance infrastructures that permit full penetration of innovative but expensive treatment strategies (e.g., ICDs).

RISK STRATIFICATION

Since the initial description of HCM, including the first contemporary report of an autopsy-based series (1), SD has been recognized as a devastating but unpredictable disease consequence; therefore, it becomes a crucial consideration in advising patients about their prognosis. Although a highly visible disease feature, SD is nevertheless confined to a relatively small subset of patients within the broad disease spectrum, most commonly young people through mid-life. SD usually occurs without premonitory warning signs or symptoms, but not uncommonly is associated with vigorous physical activity (4,8,39,40).

Recognition that the mechanism of SD in HCM is primary ventricular tachycardia and/or ventricular fibrillation (27), with the application of ICDs to this disease almost 15 years ago (27), has created the opportunity to prevent these catastrophic events for the first time. Therefore, the importance of risk stratification models to predict which individual patients would benefit most from device therapy has become increasingly relevant.

Targeting candidates for prophylactic ICD therapy can be complex, compounded by the unpredictability of the arrhythmogenic substrate, absence of a single dominant risk marker, and the impracticability of prospective randomized trials (4,8,33,34,39,40). Despite these limitations, the HCM risk stratification algorithm currently in use for primary prevention has proved effective in identifying most patients who will benefit from ICD therapy by relying largely on 5 major risk markers (4,6,8,39,40,65,76,77) (**Fig. 3**).

Although multiple risk factors in a given patient intuitively convey the greatest SD risk, there is compelling evidence that a single strong marker within the clinical profile of an individual patient (particularly in those <60 years of age) can be sufficient evidence to raise the option of a primary prevention ICD (8,28,40). These decisions are made in accord with the wishes of the fully informed patient after considering the benefits as well as the inherent possibility of device complications, including inappropriate shocks. Furthermore, strong desires of informed patients can contribute to resolution of ambiguous ICD decisions when the data are insufficient (including some involving a single risk marker); these decisions also rely on the experience and judgment of individual clinicians who adjudicate the overall risk profile (28).

Of note, the risk prediction model used in adult HCM patients is not easily translated to children, although a marked degree of LVH or syncope have proved the most reliable markers in this age group (29). Some investigators have stratified the likelihood of SD by simple arithmetic summing of risk factors, or sophisticated mathematical modeling. These approaches still require broad-based validation (20,32).

Because HCM encompasses a particularly diverse spectrum, other small high-risk patient subsets

(i.e., LV apical aneurysms [19] with regional scarring or end-stage with LV systolic dysfunction) [18] may justify consideration for primary prevention ICDs (**Fig. 3**). Disease features, such as marked LV outflow obstruction at rest or diffuse LVH with wall thickness approaching 30 mm [27,32,33], can serve as "gray zone modifiers" or arbitrators for ICD decision making on a case-by-case basis when assessment is ambiguous using conventional markers. Engagement in intense competitive sports is a modifiable SD risk factor, even in the absence of other markers, leading to disqualification to reduce risk, as recommended by Bethesda Conference #36 [57].

Notably, the absence of all risk factors does not convey immunity to SD in HCM [77]. The present risk model used in HCM is incomplete, as evidenced by infrequent SD events in diagnosed patients judged to be at low risk and ineligible for ICDs on the basis of the absence of conventional markers (approximately 0.5%/year) [77]. Recognition that seemingly low-risk patients may nevertheless die suddenly underscores the necessity to identify additional markers and/or a single quantitative risk marker (similar to ejection fraction in CAD).

These considerations have recently led to identification of a novel primary risk predictor (and arbitrator) in HCM [35]. Contrast-enhanced CMR provides an opportunity to image the substrate of presumed myocardial fibrosis. Because late gadolinium enhancement (LGE) is so common in HCM, occurring in >50% of patients, its presence alone is insufficient to risk stratify individual patients for SD. However, absence of LGE is associated with a lower risk of SD and represents a source of reassurance [35].

Conversely, SD risk is proportional to the amount of LGE, with ≥15% (of LV mass) equivalent to a 2-fold risk compared to patients without LGE [35]. Extensive LGE is a marker of SD risk, even among patients otherwise considered at low risk and who do not have established markers, but nevertheless can benefit from primary prevention ICD therapy [35].

In addition, results of contrast-enhanced CMR can resolve complex ICD decisions when the level of SD risk remains uncertain after standard stratification; that is, supporting an ICD when extensive LGE is present and constituting evidence against an ICD when LGE is absent or focal [35]. Extensive LGE also prospectively identifies HCM patients who will develop adverse LV remodeling and progress to the end stage with systolic dysfunction [35]. Therefore, CMR has emerged as a powerful addition to the HCM armamentarium, justifying a role in routine assessment of these patients by strengthening the risk stratification model. However, drug treatment with aldosterone inhibitors (i.e., spironolactone) does not appear to blunt development or progression of myocardial fibrosis in HCM [78].

IMPACT OF ICD IN PREVENTION OF SD

There is no evidence that drugs administered prophylactically (e.g., beta-blockers or verapamil) prevent SD in HCM [27-31]. The ICD is the only treatment strategy shown to prolong life in HCM due to its potential to reliably interrupt life-threatening ventricular tachyarrhythmias, and prevent sudden and unexpected death [4,27-31,39,40] (**Central Illustration**). In HCM, the ICD is effective despite substantial LVH, outflow obstruction, diastolic dysfunction, and microvascular ischemia [4,9,11,16,21,36,62,65,79,80].

Much of the available data on ICDs comes from an international multicenter registry of >500 HCM patients, in which the rate of device interventions appropriately terminating ventricular tachycardia and/or ventricular fibrillation was 4%/year for primary prevention (cumulative, 25% over 5 years), largely in asymptomatic patients, and 11%/year for secondary prevention after cardiac arrest [28] (**Fig. 3**). These effective rates are similar to those reported from numerous other centers in Europe, Australia, and the United States [30,31,34]. Furthermore, defibrillator intervention rates were similar in >200 children and/or adolescents with HCM who underwent implantation for primary or secondary prevention at <20 years of age [29]. An exception to ICD efficacy is in LAMP2 patients, who are usually refractory to defibrillation [55].

In HCM, the unpredictability of the electrical myocardial substrate is substantial, and relevant to the principle of ICD therapy. First, there is extensive variability in the time intervals between recognition of high-risk status at implantation and the initial appropriate ICD intervention, with delays of 5 to 10 years or even longer reported [28]. Also, some HCM patients have survived 10 to 20 years (up to 30 years) after cardiac arrest without a subsequent event [81]. Second, ICD shocks occur randomly during the day without defined circadian periodicity, often unassociated with physical activity and sometimes during sleep [82]. Third, there is a relationship between patient age and susceptibility to ICD interventions: uncommon after 60 years of age [38], but on average occur at about 40 years of age on average [28].

The importance of device-related complications (5%/year), including inappropriate shocks, lead defects [83], and psychosocial consequences, cannot be underestimated in HCM [27,28,31,84], particularly

with implantations early in life (29). This point underscores the importance of balancing preservation of life versus the possibility of device-related complications over time. Single-chamber ICDs are most appropriate for young high-risk patients, whereas dual-chamber ICDs are largely reserved for those with paroxysmal AF and/or LV outflow obstruction (85). Because subcutaneous defibrillators are untested in HCM, caution is warranted in considering implantation in patients with this disease (86).

ATHLETES

HCM is the most common cause of SD in the young, including competitive athletes (44,87). About one-third of athletic field deaths in U.S. high school and college students engaged in organized sports are due to HCM (15/year) (87), occurring predominantly in males without previous suspicion of disease, and most commonly in African Americans (44). These SD events provide a window to the population of HCM patients who otherwise are unrecognized and not part of clinical cohorts or the literature.

In the United States, cardiovascular screening initiatives to identify such at-risk student athletes customarily include a history and physical examination, although some screening programs in colleges have utilized 12-lead ECGs with limited success in identifying HCM (88). The American Heart Association/American College of Cardiology (AHA/ACC) do not recommend a national mandatory cardiovascular screening program (88), partly because it is unresolved whether pre-participation ECG screening reduces HCM mortality in young athletes. Measures for prevention of SD in athletes with HCM include wider dissemination of automatic external defibrillators for secondary prevention and disqualification from sports competition, according to Bethesda Conference #36 recommendations (54).

HEART FAILURE

Some degree of HF occurs in approximately 50% of HCM patients, expressed clinically as exertional dyspnea due to a variety of mechanisms, in the presence of preserved systolic function (89). However, it is rarely associated with clinical manifestations characteristic of ischemic and nonischemic cardiomyopathies (e.g., volume overload) (4). Such symptoms can be accompanied by chest pain (atypical or typical of atherosclerotic CAD), which are likely related to microvascular ischemia (79,80). Chest pain in HCM may also present as an independent clinical syndrome in which management becomes challenging, although

anecdotal evidence favors verapamil for achieving symptom benefit.

The most important cause of limiting HF symptoms in HCM is mechanical impedance to LV outflow, usually due to systolic anterior motion of the mitral valve, with gradients of ≥30 mm Hg an independent determinant of progressive HF symptoms and HF or stroke death (21) (**Fig. 4**). Outflow gradients are characteristically dynamic, with spontaneous variability influenced by altered myocardial contractility and loading conditions (2,4,11,16,21,39,40).

For patients without obstruction at rest, exercise (stress) echocardiography is the preferred method for provoking physiological gradients (16). Exercise-induced outflow gradients (≥30 mm Hg) identify patients at greater risk for future symptomatic progression, and thereby the possibility of septal reduction intervention (**Central Illustration**, **Fig. 4**). Nonphysiological provocation with pharmacological agents (i.e., amyl nitrite or isoproterenol) or the Valsalva maneuver are alternative methods for provoking subaortic gradients, although these maneuvers may not always reliably mimic the hemodynamics responsible for symptoms during daily physical activities. Cardiac catheterization may occasionally be necessary to resolve ambiguity with respect to presence and/or magnitude of gradients. In HCM, important HF symptoms are also produced by impaired diastolic filling or AF (90-93).

HEART FAILURE WITH OBSTRUCTION. Medical treatment. In HCM patients with outflow tract obstruction who develop limiting HF symptoms, the first option to control symptoms is pharmacological therapy with beta-adrenergic blockers (4-6,39,40,94) (**Central Illustration**). Although verapamil can also be considered, caution should be exercised in its administration to patients with marked resting gradients and advanced HF. LV filling can be improved by these drugs, although basal gradients are not usually mitigated significantly (4,39,40).

Beta-blockers are most effective in blunting gradients provoked with exercise (2,94). Disopyramide is the most reliable drug for reducing outflow gradients at rest in HCM, although long-term use may be limited by parasympathetic side effects (95). Current pharmacological therapy for HCM does not alter outcome or phenotypic expression. However, a number of novel drug therapies are currently being considered for testing to improve the limiting symptoms of HCM by targeting specific disease-related mechanisms (96).

Invasive therapy. Because of the duration of experience, documented long-term results, and safety
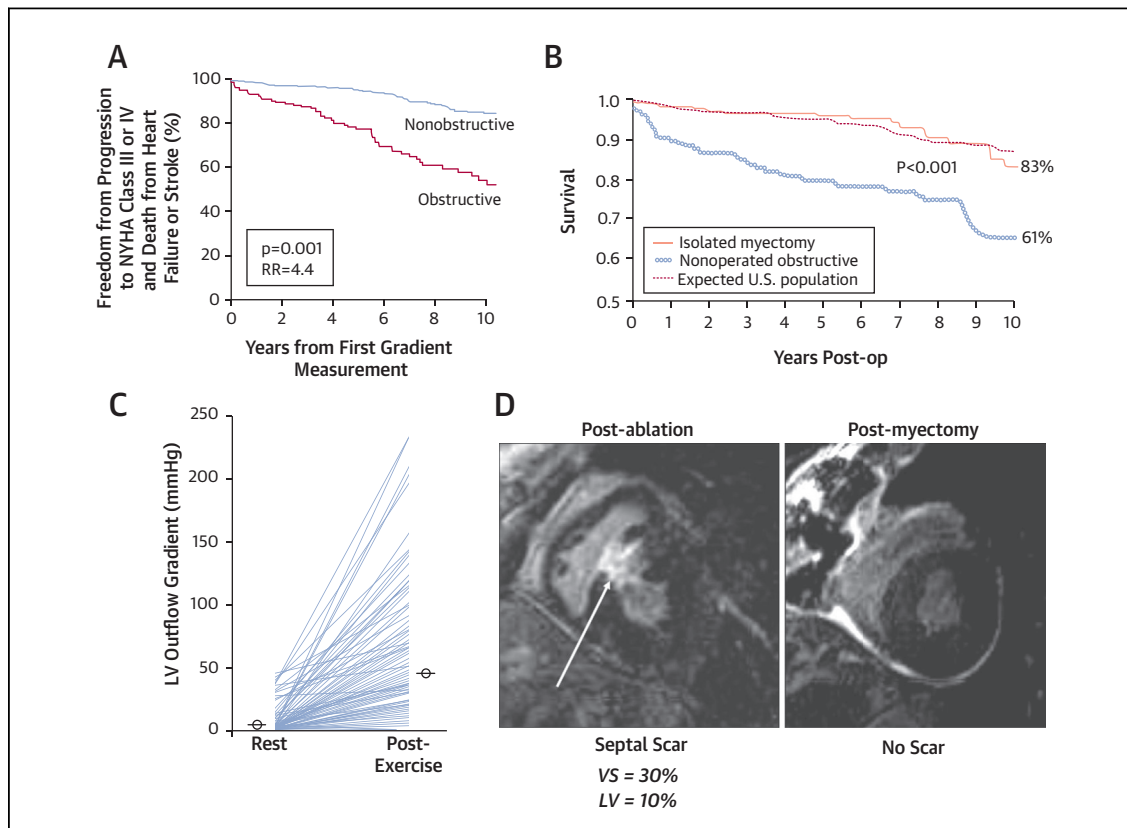
FIGURE 4 Clinical Significance and Implications of LV Outflow Tract Obstruction

(A) Patients with outflow gradients ≥30 mm Hg at rest are at greater risk for HCM-related progressive heart failure, or heart failure or stroke death. Adapted with permission from Maron et al. (21). **(B)** Abolition of LV outflow gradient by surgical septal myectomy is associated with long-term survival (with respect to all-cause mortality) similar to expected in age- and sex-matched general U.S. population, and exceeding that in a comparison group of symptomatic nonoperated patients with obstruction. Adapted with permission from Ommen et al. (36). **(C)** Most HCM patients (i.e., 70%) have LV outflow obstruction present at rest or with physiologic exercise. Some patients with only exercise-provoked gradients develop marked heart failure symptoms and also become candidates for septal reduction. Adapted with permission from Maron et al. (16). **(D)** Different morphologic consequences of alcohol septal ablation (left) and surgical septal myectomy (right) shown with post-contrast CMR images. Alcohol ablation results in a bright, dense transmural scar **(arrow)**, whereas intramyocardial scarring is absent after myectomy. Adapted with permission from Valeti et al. (106). NYHA = New York Heart Association; RR = relative risk; other abbreviations as in **Figures 1 to 3**.

data, surgical septal myectomy is considered the preferred treatment for patients with advanced limiting HF symptoms due to outflow gradients of ≥50 mm Hg (at rest and/or with physiologic [exercise] provocation) who are refractory to maximal medical management (4-6,10,13,36,39,40,97-100). This is on the basis of the expert consensus guidelines and recommendations from the ACC, AHA, and European Society of Cardiology panels (39,40).

Long-term studies over 40 years in HCM have shown that surgical myectomy reliably reverses HF symptoms by permanently abolishing obstruction, restoring normal LV pressures, and reducing or abolishing mitral regurgitation (4,10,40). Operative mortality for septal myectomy is now <1% at experienced centers (10), and the documented benefits of myectomy provide

patients with the opportunity to achieve good quality of life, extended longevity, and survival similar to that in the general population (36) (**Fig. 4**).

Percutaneous alcohol septal ablation has become an alternative to surgical myectomy (37,101-105) in selected patients (39,40). Factors that influence the decision to proceed with alcohol ablation include advanced age, significant comorbidity that increases surgical risk, or the strong desire of patients to avoid open-heart surgery (40).

Alcohol ablation reduces LV outflow gradient (and symptoms) by creating a large basal ventricular septal infarction (10% of the LV wall, 30% of the septum, on average) by infusion of absolute alcohol into a major septal perforator coronary artery (106) (**Fig. 4**). In contrast, myectomy requires resection of a small

amount of muscle from the basal septum, but without intramyocardial scarring (10,39,40). Ablation data derived from some retrospective studies show short-term survival (with respect to all-cause mortality) to be similar to myectomy and in also age- and sex-matched general populations. Procedural mortality, low in experienced myectomy programs (4,10,13,36,39,40), is similar for both interventions when performed at HCM centers (37).

However, important differences between the septal reduction procedures have emerged over 2 decades, with surgery providing better symptom and gradient improvement in patients <65 years of age. Surgery also provides the opportunity to address complex LV morphologic abnormalities that may contribute to outflow obstruction: papillary muscle anomalies and aberrant intraventricular muscle bundles; massive septal hypertrophy; intrinsic mitral valve disease (requiring repair or replacement); and associated CAD that requires bypass grafting (10,37,40).

In contrast, alcohol ablation is associated with the likelihood of permanent pacemaker implantation for complete heart block (in 10% to 15% of patients) and repeat procedures due to persistent obstruction (in 12% of patients) (101,104). There is an incompletely defined risk for life-threatening ventricular tachyarrhythmias and SD due to the potentially arrhythmogenic septal scar, which was reported as significant in 3 single-center studies (102,103,105) and the Multicenter North American Registry (107). No risk stratification model for prophylactic ICD implantation following ablation has been proposed.

Optimally, both myectomy and alcohol ablation should be performed in multidisciplinary centers with extensive HCM treatment experience and demonstrable high success and low procedural mortality rates, with the selection of either procedure balanced and unbiased in accord with autonomy of the fully informed patient (40). A randomized trial comparing myectomy versus alcohol ablation is impractical and unrealistic (108). Dual-chamber pacing was promoted with enthusiasm in the 1990s as an alternative to surgery (109), but it has been largely abandoned on the basis of double-blind crossover trials that showed the perceived symptomatic benefit was largely a placebo effect (110).

HEART FAILURE WITHOUT OBSTRUCTION. About one-third of HCM patients have the nonobstructive form with absent or small (<30 mm Hg) outflow gradients at rest and with physiological exercise (16). The majority of nonobstructive HCM patients experience a relatively stable clinical course without significant symptoms, high-risk profile, or the necessity of major treatment options (111).

Only a minority of nonobstructive patients will experience progressive, limiting HF symptoms predominantly due to diastolic dysfunction (111) (**Central Illustration**). Medical treatment is limited to atrioventricular nodal blocking agents (and possibly low-dose diuretics) that may exert a beneficial effect on diastolic function by increasing myocardial blood flow and LV filling time, but often without long-term efficacy. The clinical severity of diastolic dysfunction in HCM is difficult to assess directly because noninvasive measures of diastolic function do not accurately reflect LV filling pressures (112).
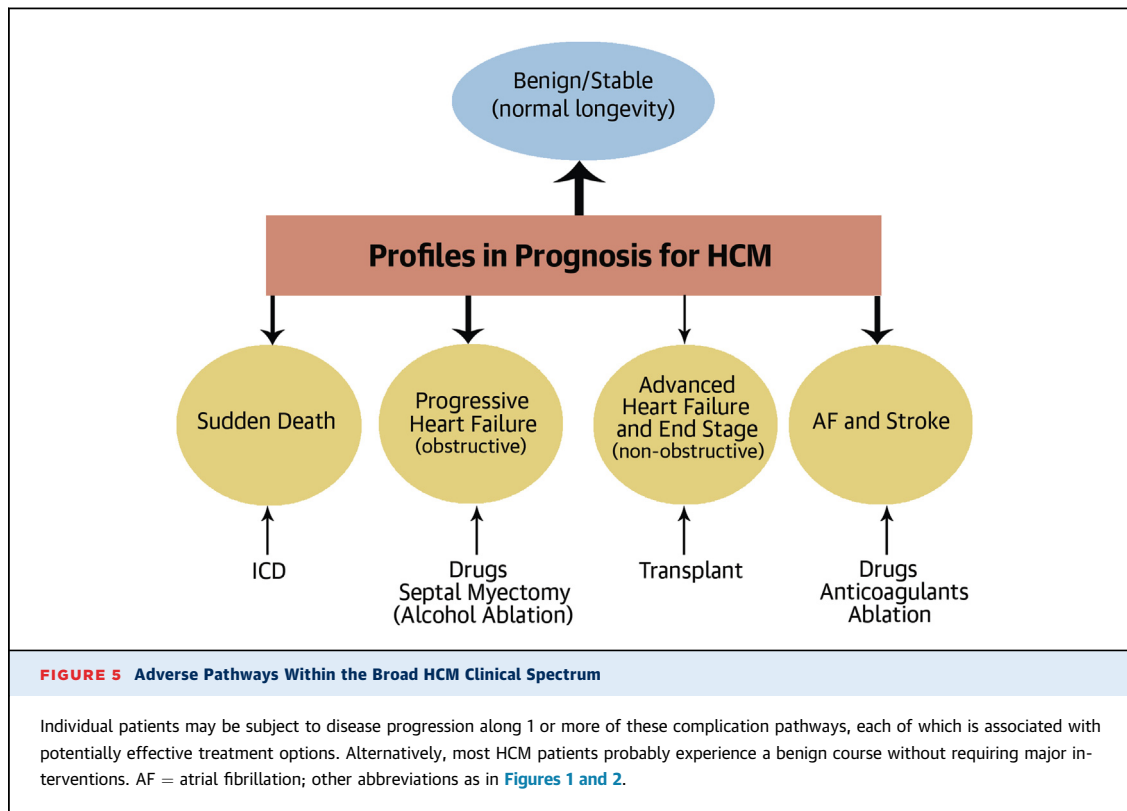
The most advanced form of HF within the HCM spectrum is the end-stage (or "burned out") phase occurring in a distinctive subset of patients with nonobstructive HCM (prevalence, 3%) (18). HF progression is associated with conversion to systolic dysfunction (ejection fraction <50%) and adverse LV remodeling with extensive myocardial scarring, often resulting in regression of hypertrophy and/or cavity enlargement (35,113). Initial treatment considerations are beta-blockers, diuretics, and afterload reducing agents, as well as prophylactic ICDs.

The clinical course of end-stage patients is variable and unpredictable, but HF symptoms may progress rapidly in some, suggesting the prudence of early listing for transplantation. This remains the only definitive therapeutic option for this relatively young patient group (average age, 43 years) (18). Post-transplantation survival (75% at 5 years; 60% at 10 years) is similar or possibly more favorable than that for patients with other cardiac diseases (114). The only known predictor of end-stage HCM is a family history of end-stage disease. A small subset of nonobstructive HCM patients with preserved systolic function who develop refractory HF symptoms due to diastolic dysfunction can also become heart transplantation candidates.

ATRIAL FIBRILLATION

GENERAL CONSIDERATIONS. Although it is rarely the initial manifestation of HCM, AF (or atrial flutter) represents the most common disease complication and sustained arrhythmia, occurring in 25% of patients, which is 4-fold more common than in the general population (90–93). Asymptomatic and clinically silent periods of this arrhythmia are not uncommonly detected by random ambulatory monitoring. Most common are paroxysmal episodes, although AF may become permanent over time in a minority of patients.

Susceptibility to AF is linked to increasing age, greater left atrial volume and/or impaired left atrial

FIGURE 5 Adverse Pathways Within the Broad HCM Clinical Spectrum

Individual patients may be subject to disease progression along 1 or more of these complication pathways, each of which is associated with potentially effective treatment options. Alternatively, most HCM patients probably experience a benign course without requiring major interventions. AF = atrial fibrillation; other abbreviations as in **Figures 1 and 2**.

ejection fraction (115). AF onset is at 55 years on average, ≥10 years earlier than in the general population, but is rare in children and young adults. AF may not be well tolerated when associated with LV outflow tract obstruction, and not uncommonly occurs in patients with systolic dysfunction and advanced HF (end-stage) (18,90).

AF and left atrial remodeling are inter-related and independent predictors of adverse outcome in HCM (90–93). Frequent paroxysmal AF episodes (or chronic AF) may negatively impact quality of life, accounting for unexpected hospital admission, lost work and productivity, and is often associated with progressive HF. The pattern of occurrence and the number of symptomatic AF episodes are unpredictable and vary considerably among individual patients. However, whether infrequent AF reliably predicts unfavorable long-term consequences is unresolved. Patients with AF usually experience no or mild symptoms while in sinus rhythm, unless associated LV outflow obstruction is responsible for exertional dyspnea. No clinically relevant relationship has been reported between AF and SD (90).

MANAGEMENT. Relatively infrequent AF episodes are effectively reversed by electrical or pharmacological cardioversion (or resolve spontaneously), but occasionally can trigger acute clinical decompensation.

Low-dose amiodarone is generally regarded as the most effective agent for reducing AF recurrences, although it frequently has side effects that limit its use over time, particularly in young patients. Alternative antiarrhythmic drug therapy includes sotalol or possibly disopyramide in the presence of obstruction.

HCM patients with AF have an increased risk of thromboembolic stroke, 0.8%/year (91). Because of the potential for clot formation in the enlarged left atrium, stroke prevention is initiated by prophylactic anticoagulation with warfarin or newer oral agents (i.e., dabigatran or rivaroxaban), tailored to individual patients after consideration for lifestyle modifications, hemorrhagic risk, and expectation for compliance. An aggressive posture with a low threshold for intervention with anticoagulation has been recommended for all patients with symptomatic AF episodes, given that the CHADS score is not specifically validated or useful in this disease.

When quality of life is significantly affected by frequent symptomatic AF episodes in drug-refractory patients, the option of catheter-based ablation (radiofrequency or cryoablation) has proved promising (92,116,117). Although relatively early in its development, catheter ablation provides the potential for prolonged restoration of sinus rhythm, although the selection of patients with the greatest likelihood of

benefit remains challenging. Current data in HCM suggest that two-thirds of patients maintain sinus rhythm for 3 years, although a substantial proportion may require ≥2 procedures, with most continuing on antiarrhythmic drugs and anticoagulation (116,117). For severely symptomatic patients with outflow obstruction and AF, combining myectomy with the Maze procedure has been suggested, although the efficacy of this practice is unknown.

CONCLUSIONS

For many years, HCM was considered a rare and unusual condition, largely without effective management strategies, and particularly devoid of treatment options for SD risk. As cardiovascular medicine has evolved over the last 2 decades (principally focused on atherosclerotic CAD), advances in diagnosis and management have been translated into genetic heart diseases such as HCM. The efforts of many investigators in different parts of the world have more precisely defined the clinical and morphological spectrum and natural history of HCM, and captured its exceptional heterogeneity, complexity, and unpredictability.

At this juncture, based on the effective use of ICDs for primary prevention, heart transplantation for refractory HF, advances in the surgical treatment of outflow tract obstruction now associated with low risk and excellent long-term outcome, and out-of-hospital defibrillation techniques (including therapeutic hypothermia) (118), it is appropriate to regard the evolution of HCM in 2014 as a paradigm shift to a contemporary treatable disease (119) (**Fig. 5**). These advances now provide a substantial proportion of individuals affected by HCM with the opportunity to achieve normal or extended life expectancy without disability or the requirement for major treatment interventions to achieve that outcome.

Although HCM deserves greater optimism from the cardiovascular community than in previous eras, it nevertheless remains a complex disease entity with the need for continued focused investigation to meet a number of future challenges. Although the ICD is a proven measure for preservation of life in HCM, the need to more precisely identify which patients will benefit from this therapy remains a critical issue. Pharmacological therapy to control symptoms of HF has remained unchanged over many years and requires innovation to identify novel agents tailored to HCM. Although the molecular era has provided the opportunity to perform rapid genetic testing to identify family members at risk of developing HCM, the genetic substrate remains unresolved for a substantial proportion of patients. Finally, there is a need to better understand the structural and metabolic derangements caused by the pathogenic mutations to allow novel therapies to be developed that target key pathways of disease progression.

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